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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
HUI, SAN MING R	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAJESH MANCHANDA

Appeal 2008-0609
Application 09/855,542
U.S. Patent Application Publication 2002/0187099
Technology Center 1600

Decided: April 23, 2008

Before FRED E. McKELVEY, *Senior Administrative Patent Judge*, SALLY GARDNER LANE, and MICHAEL P. TIERNEY *Administrative Patent Judges*.

LANE, *Administrative Patent Judge*.

DECISION ON APPEAL

I. STATEMENT OF THE CASE

The appeal is from a Final Rejection of claims 1-4, 6, 8,-10 and 32-33. 35 U.S.C. § 134. We have jurisdiction under 35 U.S.C. § 6(b). We affirm. The application was filed May 16, 2001. It was published as U.S. Patent Application Publication 2002/0187099 ("Pub. 2002/0187099") on December 12, 2002. The real party in interest is said to be CIS Bio International (Saclay, France). (App. Br. at 1).

Appellant appeals the rejection of claims 1-4, 6, 8-10, 32, and 33 under 35 U.S.C. § 103 as being unpatentable over Solanki and Cyr. In the Appeal Brief, Appellant argued the patentability of claims 1, 4, 6, 8-10, 32, and 33 as a group. Appellant argued claims 2 and 3 as being separately patentable.

The following U.S. Patents were relied upon by the Examiner:

Name	Patent No.	Issue Date
Solanki	US 5,262,175	Nov. 16, 1993
Cyr	US 6,881,396	Apr. 19, 2005

Appellant did not dispute the status of either of these references as prior art.

II. FINDINGS OF FACT

The record supports the following findings of fact, as well as any other findings of fact set forth in this opinion, by at least a preponderance of the evidence.

1. Appellant's specification is drawn to "methods for stabilizing radionuclide-containing compositions against degradation caused by free radicals generated from the radionuclide or other forms of radiolysis." (Pub. 2002/0187099 at ¶ [0001]).
2. Appellant's claim 1 recites[1]:

A composition comprising:
- (1) a radionuclide, excluding iodine radionuclides,
- (2) a targeting agent, and
- (3) iodide ions or a compound which releases or generates iodide ions, where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition, and, where the targeting agent:
- is a peptide, oligonucleotide, antibody or peptidomimetic, or

[1] Claim 1 has been reformatted to add reference numbers in parentheses.

- is a targeting agent bonded to a complexing moiety, of the following formula:
A--CZ(B)---[C(R^1R^2)]$_n$-X
wherein
A is H, HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC or R^4;
B; is H, SH or –NHR3, -N(R^3)-(peptide, oligonucleotide, antibody or small organic compound) or R^4;
X is SH or –NHR^3,- N (R^3)-(peptide, oligonucleotide, or antibody) or R^4;
R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl;
n is 0, 1 or 2; and,
Z is H, SH or R^4;
provided that:
(a) where B is –NHR^3 or - N(R^3) - (peptide, oligonucleotide, or antibody), X is SH and n is 1 or 2;
(b) where X is –NHR^3 or -N(R^3)-(peptide, oligonucleotide, or antibody), B is SH and n is 1 or 2;
(c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC, X is SH and n is 0 or 1;
(d) where A is H or R^4, then, where B is SH, X is –NHR^3 or - N(R^3) - (peptide, oligonucleotide, or antibody) and where X is SH, B is –NHR^3 or - N(R^3) - (peptide, oligonucleotide, or antibody);
(e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH;
(f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH and n is 0; and
(g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, or antibody.

3. Appellant's specification teaches that it was known in the art to use radionuclides for diagnostic and therapeutic purposes, such as labeling peptides, wherein

> [c]ompounds, compositions and complexes containing radionuclides have been known for diagnostic and therapeutic applications. Among such embodiments [*i.e.*, the compounds, composition and complexes containing radionuclides that have been known for diagnostic and therapeutic applications] are reagents having one or more components for binding a radionuclide, such as technetium-99m ("Tc-99m"), and a component for targeting the reagent to a specific site in the body, such as a mammalian body, particularly human . . . . Examples of such reagents are described in U.S. patents 5,783,170; 5,807,537; 5,814,297; and 5,866,097. Particularly disclosed as reagents are complexes of the radionuclide with a complexing group which complexes the radionuclide and which is covalently bonded to a specific binding peptide for targeting the complex.

(Pub. 2002/0187099 at ¶ [0002]).

4. Like Appellant's specification, the specification of Cyr also teaches increasing the efficiency and shelf-life of peptide and non-peptide radiopharmaceutical compositions. (Cyr at col. 2, ll. 35-37).
5. Like Appellant's specification, Cyr teaches stabilizers of radiopharmaceutical compositions, though Cyr teaches compounds called hydrophilic 6-hydroxy-chromans. (Cyr at col. 1, ll. 23-28).
6. In Example 1 of Appellant's specification, potassium iodide is described as having been added to a radionuclide-peptide complex called Tc-99m depreotide. (Pub. 2002/0187099 at ¶ [0018]-[0019]).
7. Appellant's specification concludes that Example 1 shows "KI affords stability to Tc-99m depreotide even when an oxidant (i.e.

nitrate) is present in the eluate [the solution which generates Tc-99m]." (*Id.* at ¶ [0019]).

8. Example 2, Table 1, of Appellant's specification reports that "[i]odide was added to the composition containing the targeting agent (peptide) and formulated as a single vial kit. The kit was reconstituted with Tc 99m to produce Tc 99m complexed to the targeting agent." (*Id.* at ¶ [0020]).
9. Example 2, Table 2, of Appellant's specification reports that "[i]odide was added to a formulated kit that contained the targeting agent (peptide) followed by the addition of the radionuclide (Tc-99m) to produce Tc 99m complexed to the targeting agent." (*Id.* at ¶ [0021]).
10. Appellant's conclusion from the studies provided in Example 1 is that "various amounts of iodide ions added either as part of a formulated kit with the targeting agent (single vial) or added to a formulated targeting agent prior to the addition of the radionuclide (2-vial), afford stabilization of the composition." (*Id.* at ¶ [0022]).
11. The composition recited in claim 1 is not limited by the order of addition of the radionuclide, targeting agent, or iodide ions.
12. Solanki teaches stabilization of radionuclides complexed to pharmaceutical compositions. (Solanki at col. 1, ll. 7-8).
13. The specific radionuclide disclosed by Solanki is Tc-99m provided in an eluate. (Solanki at col. 4, ll. 28-32).
14. Solanki teaches that it was known in the art to add "sodium iodide to the fresh eluate per vial of [a targeting agent to] overcome the eluate age restriction." (Solanki at col. 7, ll. 40-42).

15. Similarly, Solanki describes a study wherein "[a]n experiment was carried out in which sodium iodide was added to fresh eluate from a generator eluated in the previous 24 hours." (Solanki at col. 7, ll. 55-57).
16. The conclusion drawn in Solanki from the study adding sodium iodide and other studies on the stabilization of radionuclide complexes was "that incorporating each step of development (freezing, addition of sodium hypochloride, and *the addition of sodium iodide to the eluate*) neutral-lipophilic kit of Tc-99m [targeting agent] could be stablised [sic] for use up to eight hours after reconstitution with Tc-99m pertechnetate using the above procedure." (Solanki at col. 8, ll. 16-22) (emphasis added).
17. The targeting agent disclosed in Solanki is not a peptide, oligonucleotide, antibody, or peptidomimetic, as claimed, but instead is a lipophilic compound. (Solanki at col. 1, ll. 7-11).
18. Another aspect of the invention disclosed in Solanki is "a method of stabilising a Technetium 199m neutral lipohilic complex containing stannous ions by the addition of a weak oxidising agent." (Solanki at col. 2, ll. 20-22).
19. Appellant's specification provides:

> The iodide ion used for stabilization according to the invention may be derived from any known source. Particularly useful are iodide salts which provide the iodide ion in solution and which are biocompatible. Most preferred are alkali metal iodide salts, particularly KI and NaI.

(Specification at 4).

III. ISSUES

The issue is whether Appellant has shown that the Examiner erred in rejecting claims 1-4, 6, 8-10, 32, and 33 under 35 U.S.C. § 103(a) as being unpatentable over Solanki and Cyr.

IV. LEGAL PRINCIPLES

"[C]laims yet unpatented are to be given the broadest reasonable interpretation consistent with the specification during the examination of a patent application since the applicant may then amend his claims . . . ." *In re Prater*, 415 F.2d 1393, 1404-05 (C.C.P.A. 1969). Claims are to be interpreted in light of the supporting specification, but limitations of the specification should not be read into a claim where no express statement of the limitation is included in the claim. *See id.* at 1396.

To determine whether subject matter would have been obviousness, we look to "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. . . . Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

The Supreme Court has noted that a combination of references renders claimed subject matter obvious under 35 U.S.C. § 103

> [w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007). Moreover, "[c]ommon sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 1742. A finding that elements of a claimed invention work "together in an unexpected and fruitful manner" can support a conclusion of non-obviousness. *Id.* at 1740.

If prior art references are combined to show that the claimed subject matter would have been obvious, the references must demonstrate that the combination presents a "reasonable likelihood of success" in producing the claimed subject matter. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

If Appellant can point to factors known by those in the art that would have deterred investigation into the combination of references, the combination may not have been obvious. *See United States v. Adams,* 383 U.S. 39, 52 (1966).

V. ANALYSIS

Appellant's specification is drawn to compositions that result from stabilization of radionuclides complexes. (FF[2]1). As provided in claim 1, the stabilized compositions comprise the radionuclide, a targeting agent, and iodide ions or a compound that releases or generates iodide ions. (FF 2).

Claim 1 recites several types of targeting agents, including peptides. (FF 2). Appellant's specification confirms that complexes between radionuclides and peptides were known in the art before the instant application was filed. (FF 3). The Examiner cited Cyr, which, consistent

[2] Finding of Fact.

with the Appellant's specification, discloses radiopharmaceuticals that include protein and peptide targeting agents. (FF 4). In addition, Cyr teaches stabilizing radionuclide peptide compositions, though with reagents which are different from the iodide ions or compounds that release or generate iodide ions recited in Appellant's claim 1. (FF 5).

To demonstrate the use of iodide ions in stabilization of radionuclide-targeting agent complexes, Appellant's specification provides Example 1, in which potassium iodide was reportedly added to a radionuclide-peptide complex called "Tc-99m depreotide." (FF 6). Appellant notes that in this study "KI affords stability to Tc-99m depreotide even when an oxidant (*i.e.*, nitrate) is present in the eluate" (FF 7), wherein the eluate is the solution that generates Tc-99m. Similarly, Appellant's Example 2 reports two studies in which either potassium iodide or sodium iodide was added to the peptide depreotide followed by the addition of a radionuclide. (FF 8 and FF 9). From both studies, Appellant drew the conclusion that the iodide ions "afford stabilization of the composition." (FF 10). Thus, Appellant teaches that the iodide ions stabilize the radionuclide-targeting agent complex, regardless of whether the iodide ions are added to the targeting agent before the radionuclide is added to form the complex or are added to the radionuclide-peptide complex after it is formed. Like Appellant's specification and Cyr, Solanki teaches stabilization of radionuclides complexed to pharmaceutical compositions. (FF 13). Also like Appellant's specification, Solanki teaches forming complexes with the radionuclide Tc 99m provided in an eluate. (FF 13). Solanki teaches that it was known in the art to add sodium iodide directly to the radionuclide eluate to "overcome the age restriction" (FF 14) or stabilize it. Solanki additionally discloses

studies in which sodium iodide is reportedly added to the eluate (FF 15) and draws the conclusion that the addition of the sodium iodide, among other steps such as freezing, stabilized the Tc-99m-targeting agent complexes for up to eight hours. (FF 16).

While the addition of sodium iodide to stabilize radionuclide-targeting agents reported in Solanki mirrors that claimed by Appellant, the targeting agents differ. Solanki teaches only targeting agents that are lipophilic compounds, not peptides, oligonucleotides, antibodies, or peptidomimetics. (FF 17). As Appellant's specification states and Cyr discloses, complexes between radionuclides and peptides were known in the art before Appellant's filing date. Because those in the art would have reason to combine the radionuclide stabilization with iodide reported in Solanki with the formation of radionuclide-peptide complexes in Cyr, we find no error in the Examiner's *prima facie* case for obviousness of the claimed composition.

Appellant argues that the *prima facie* case is faulty because Solanki also teaches that weak oxidizers stabilize radionuclide complexes and that these weak oxidizers are "specifically selected to stabilize this type of lipophilic complex with these type of complexing agents." (App. Br. at 4). According to Appellant, there is no reasonable expectation of successful use of weak oxidizing agents with non-lipophilic radiopharmaceuticals from the teachings in Solanki. (*Id.* at 5). In contrast to Solanki, Appellant notes that "Cyr discloses using an anti-oxidant agent to stabilize radiopharmaceuticals with particular emphasis on those having peptide-based targeting agents." (App. Br. at 5). Appellant summarizes:

> Solanki's purpose is to provide a weak oxidizing effect to stabilize certain types of lipophilic radiopharmaceuticals and Cyr's purpose is to provide an anti-oxidant effect to stabilize

> other types of radiopharmaceuticals, particularly ones with peptide complexing agents. Although both have the ultimate purpose of stabilizing a radiopharmaceutical, such purpose is achieved in distinct ways such that one of ordinary skill in the art would not expect interchangeability of the agents.

(*Id.* at 6).

It is true that one portion of Solanki is specifically directed to the stabilization of radionuclide-lipophilic complexes with weak oxidizing agents. (FF 18). However, another portion of Solanki teaches stabilization of the radionuclide portion of these complexes by adding sodium iodide to the Tc-99m eluate, before any targeting agent is added to the complex. (FF 12-16). Indeed, as Appellant acknowledges, Solanki teaches sodium iodide is "added to the Tc-99m pertechnetate eluate solution – before the radionuclide is combined with the complexing/targeting agent – to overcome the age restriction on the eluate." (App. Br. at 7). Thus, those in the art would have had a reasonable expectation of success in stabilizing the radionuclide as taught in Solanki and then complexing it to a peptide, as in Cyr, to achieve a more stable complex overall.

Furthermore, Appellant's arguments regarding the different methods of stabilizing radionuclide-targeting agent complexes taught by Solanki and Cyr (App. Br. at 6) do not in any way undermine Solanki's teaching of stabilization of the radionuclide itself. To the extent Appellant's argument is that one skilled in the art would not have had a reason to select iodide ions to stabilize the radionuclide-peptide complex of Cyr because Solanki teaches using iodine to stabilize a radiopharmaceutical complex as a whole, the argument is not convincing. Claim 1 is not limited to a method of stabilizing the complex. (FF 11). Instead, claim 1 is directed to a

composition containing iodide ions or an iodide ion-releasing or generating compound. Furthermore, Solanki teaches that iodide stabilizes the radionuclide, thus stabilizing the entire complex.

Appellant also argues that the addition of sodium iodide taught in Solanki is not relevant to the claimed composition because col. 7, ll. 31, to col. 8, ll. 50, of Solanki "relates to preparing the eluate and teaches 'sodium iodide was added to the fresh eluate,'" (Reply Br. at 1). Appellant's claims, though, do not distinguish between a composition with iodide ions added to the radionuclide before or after complexing with the targeting agent. (FF 11).

Finally, Appellant argues that "the combination of Solanki with Cyr would additionally be distinct from Appellant's invention in failing to disclose a composition or method containing 'iodide ions or a compound which releases or generates iodide ions'" (App. Br. at 6), since Solanki (at col. 2, ll. 5-7), provides: "Further halogen releasing agents which can be employed are iodine, iodophores and providone-iodine." According to Appellant "[t]he suggestion to use <u>iodine</u> as the oxidizing agent in Solanki is not equivalent to or suggestive of the use of <u>iodide</u> ions. The term 'iodine' can be used to describe the element I, but is clearly used in Solanki as describing the compound I_2." (App. Br. at 6). Even if Appellant is correct, that Solanki's reference to iodine as a weak oxidizing agent means I_2, as discussed *supra* Solanki also teaches that iodide ions contribute to stabilization of radionuclide complexes. In particular, Solanki teaches metal salts, NaI and KI, which are the same as those disclosed in Appellant's specification. (FF 19).

On the record before us, one skilled in the art would have had reason to add an iodide ion or iodide ion-releasing compound to a known (as acknowledged by Appellant and shown by Cyr) radionuclide-peptide complex since Solanki teaches that the compound stabilizes the radionuclide portion of the complex. Appellant has not offered rebuttal evidence of unexpected results or any other secondary considerations. *Cf. In re Sullivan*, 498 F.3d 1345, 1352 (Fed. Cir. 2007). On this record, we conclude that the Appellant has not shown that Examiner erred in rejecting claims 1, 4, 6, 8-10, 32, and 33 under 35 U.S.C. § 103 over Solanki and Cyr.

Claims 2 and 3

Appellant separately argued the patentability of claims 2 and 3. Claim 2 depends from claim 1 and includes the limitation "wherein the iodide ions are provided by an iodide salt in the composition." Claim 3 also depends from claim 1 and adds the limitation "wherein the iodide ions are provided by an alkali metal iodide salt in the composition." Appellant argues that

> even if it were considered that Solanki's disclosure of the use of iodine as a weak oxidizing agent would provide iodine ions and that it would be obvious to use iodine to stabilize the radiopharmaceutical compositions of Cyr – both points being disputed above – such a conclusion would still not suggest to one of ordinary skill in the art the use of an iodide salt or alkali metal iodide salt for such stabilization.

(App. Br. at 8). As we found above regardless of Solanki's suggestion of iodine as a weak oxidizing agent at col. 2, ll. 5-7, Solanki also expressly teaches that sodium iodide added to the eluate stabilizes the radionuclide of the complex. (FF 12-16). As Appellant has acknowledged, sodium iodide is an iodide salt, specifically an alkali metal iodide salt. (FF 19). Accordingly,

we conclude that Appellant has not shown that the Examiner erred in rejecting claims 2 and 3 under 35 U.S.C. § 103.

VI. ORDER

Upon consideration of the record and for the reasons given, the Examiner's rejection of claims 1-4, 6, 8-10, 32, and 33 under 35 U.S.C. § 103(a) over Solanki and Cyr is AFFIRMED.

AFFIRMED

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John A. Sopp, Esq.
MILLEN, WHILE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Blvd., Suite 1400
Arlington, VA 22201